# Drug Compounding for Veterinary Patients

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## ABSTRACT

Drugs have been compounded for veterinary practice for many years because it has been necessary in the course of routine practice. However, regulations and compliance policy guidelines (CPGs) should be recognized. A new CPG issued in July 2003 listed the current Food and Drug Administration (FDA) limitations on compounding for veterinary medicine. To summarize the guideline: drugs must not be compounded from bulk substances, and the compounding must not constitute manufacture of a new animal drug. Drug compounding on a case-by-case basis is allowed under the CPG. However, veterinarians and pharmacists must be aware of potential incompatibilities and practices that may interfere with the drug's stability, purity, and/or potency.

**Keywords:** compounding, veterinary drugs, *USP*, extra-label drug use

## CURRENT REGULATIONS ON COMPOUNDED VETERINARY DRUGS

Drug compounding has always been a part of veterinary medicine. Historically, veterinarians have been known for preparing concoctions, mixtures, and remedies for their patients because there were few approved veterinary formulations on the market. Now, however, there are more available drugs for use in animals, and scientists have acquired a better understanding of factors influencing the risks of drug instability as well as the incompatibility of certain mixtures. Concerns regarding the widespread practice of product compounding have been raised with respect to drug stability, purity, and potency.

Compounding is the alteration of the original drug dosage form for the purposes of ease of administration or because the original dosage form is unsuitable for the purpose intended. According to the *United States Pharmacopeia (USP)*,[1] compounding involves the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription. The *USP* chapter on pharmacy compounding states that "compounding is an integral part of pharmacy practice and is essential to the provision of health care."[1]

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Although the Food and Drug Administration (FDA) does not currently define compounding, in a previous CPG compounding was listed as, "any manipulation to produce a dosage form drug other than that manipulation that is provided for in the directions for use on the labeling of the approved drug product."[2] Compounding does not include the preparation of a dosage form by reconstitution or mixing if conducted in accordance with FDA-approved manufacturer's instructions on an approved human or veterinary product label.

In 1993, a symposium on compounding in veterinary medicine was held by the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT).[3] This symposium had representatives from the American Veterinary Medical Association (AVMA), FDA/CVM (Center for Veterinary Medicine, CVM), pharmacology and pharmacy groups, and the USP. The symposium provided the opportunity to hear the diverse perspectives held by practitioners, pharmacologists, regulatory officials, pharmacists, and lawyers. The product of this symposium was a task force report that summarized the presentations and resulted in the Compliance Policy Guide (CPG) published in 1996.[2] The proceedings from this symposium are very informative and contain 115 pages of presentations, which cannot be adequately summarized here.

The FDA recently revised this CPG for compounding drugs for use in animals.[4] The new CPG provides guidance to FDA's staff with regard to the compounding of animal drugs by veterinarians and pharmacists for use in animals. This CPG is available from the FDA, or on the Internet (www.fda.gov/ora/compliance_ref/cpg/default.htm).

The FDA recognizes a necessity for compounding in veterinary practice but must ensure that compounded drugs do not cause harm to treated animals, are not associated with therapeutic failure resulting from a lack of product potency, and do not cause violative residues in food-producing animals. While FDA regulations permit the compounding of formulations from approved animal or human drugs (21 CFR 530.13) (legislation available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=530.13), the FDA needs to ensure that compounding by veterinarians and pharmacists is not performed in an effort to circumvent the usual drug approval process. Some compounding practices (eg, mass production and labeling of some products) constitute manufacturing and distributing of new animal drugs. Under these circumstances, there is little or no quality con-

trol or assurances of stability, purity, and potency, which violates the federal code. Therefore, compounding is limited to the preparation of drug products that do not meet the definition of new animal drugs. For example, the FDA permits compounding on a case-by-case basis and on the order of a veterinarian when there is a need for an appropriate size oral dosage form to produce a more palatable oral drug, to produce a more dilute formulation for a small animal or exotic animal patient, or when it is necessary to admix anesthetics for ease of administration. These are expected practices and will not be subject to regulatory action according to the most recent CPG.

The new CPG, published in July 2003, available at www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg608-400.html, was specifically intended to clarify the regulations on compounding from unapproved or bulk drugs. "Bulk drugs" are defined as active ingredients used in the manufacture of finished dosage forms. Compounding from bulk drugs or from unapproved drug substances is not allowed. However, the CPG provided a list of compounds for which compounding from a bulk substance ordinarily would not be subject to regulatory action. Although most of the compounds in Appendix A are obsolete and not used currently in veterinary medicine, compounding of these latter compounds is allowed in instances where the health of the animal is at risk and when no other remedies are available. The list includes antidotes such as methylene blue or sodium nitrite. A complete list of allowed bulk drugs is listed in the CPG for compounding drugs for use in animals.[4]

Large scale compounding from bulk drugs has been practiced by some pharmacies importing large quantities of raw chemicals. The FDA has seized compounded products from bulk drugs and has issued warnings to pharmacies when there have been regulatory violations.[5] In August 2004, the FDA seized compounded drugs from a pharmacy that was supplying medications for horses (www.avma.org/onlnews/javma/oct04/041001a.asp). Despite these seizures and warnings, this practice continues to occur, and products are still advertised in plain sight at national trade shows and on the Internet without penalty. In reaction to this situation, some organizations have taken steps to discourage illegal compounding. The *Journal of the American Veterinary Medical Association* recently adopted an editorial policy stating it will not publish papers in which illegal compounded drugs are used in a research study.

The current CPG has been controversial. Lawsuits have been filed against the FDA because of the current policy on bulk drugs. The International Academy of Compounding Pharmacists has launched a campaign to encourage the FDA to withdraw the CPG and is lobbying Congress to help change the FDA's policy on compounding from bulk drugs (www.avma.org/onlnews/javma/oct04/041001a.asp). The FDA announced that it would revise the current CPG sometime in the fall of 2004 (www.avma.org/onlnews/javma/oct04/041015c.asp), however at the time of this article, an update was not available and this continues to be an on-going and controversial issue.

## The Need for Compounded Drugs in Veterinary Medicine

Palatability, ease of administration, and dispensing factors are among the considerations used when formulating drugs for animals. Drugs intended specifically for animals and registered by the FDA are designed with great care. Pastes and dosage syringes are available for some drugs used in horses. Flavored tablets are often available for dogs to ease administration by pet owners. To prevent parasite infestations, transdermal medications are available for dogs and cats to avoid the necessity of frequent administration to a pet that may be difficult to medicate. One of the largest costs to pharmaceutical companies when developing new drug products is the determination of an appropriate formulation. When companies spend literally millions of dollars "getting the formulation right" in terms of stability, solubility, and palatability, it is risky to expect that new drug formulations compounded in a pharmacy will have the same assurance of stability, purity, and potency.

Sometimes, compounding is a necessity. Despite advances in new drugs available for animals, many unmet needs still remain. Therefore, many drugs are crossed over from one animal species to another, or are human drugs administered to animals. According to a 1999 survey,[6] the top 10 drugs that are compounded for veterinary medicine are potassium bromide, metronidazole suspension, methimazole oral liquid, diethylstilbestrol capsules, cyclosporine ophthalmic solution, prednisone oral liquid, amitriptyline oral liquid, chloramphenicol oral suspension, and protamine zinc insulin. Much of the compounding cited in the survey consisted of mixing drugs with various foods and flavorings in an effort to ease product administration to hard-to-medicate pets or exotic species.

## Potential Problems Caused by Compounded Formulations

Some compounded drug formulations can present problems if the safety and potency of the compounded product have not been considered. Tablets that must be crushed or broken to deliver a smaller dose size to dogs or cats may be unpalatable for oral use in animals. When drugs are administered to cats, either a portion of a tablet must be given, or the drug is reformulated into a capsule. Because ill cats are usually anorectic and because cats generally do not drink water frequently, solid dose forms have become trapped in the esophagus of cats. The latter problem was documented in 2 studies in which capsules were orally administered to cats. When

**Table 1.** Signs of Drug Instability of Compounded Formulations

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|---|
| **Liquid Dose Forms** |
| Color change (pink or amber) |
| Signs of microbial growth |
| Cloudiness, haze, flocculent, or film formation |
| Separation of phases (eg, oil and water, emulsion) |
| Precipitation, clumping, crystal formation |
| Droplets of fog forming on inside of container |
| Gas or odor release |
| Swelling of container |
| **Solid Dose Forms** |
| Odor (sulfur or vinegar odor) |
| Excessive powder or crumbling |
| Cracks or chips in tablets |
| Swelling of tablets or capsules |
| Sticking together of capsules or tablets |
| Tackiness of the covering of tablets or capsules |

capsules containing barium sulfate were followed radiographically, they became entrapped in the midcervical region of the esophagus 53% of the time.[7] These capsules pass into the stomach when followed by food. In another study, a dry capsule given to cats was retained in the esophagus for greater than 300 seconds 63% of the time. (Recordings were not made after 300 seconds.) Wet capsules passed 97% of the time at 30 seconds and 100% of the time thereafter.[8] The location of the entrapment of capsules is particularly disturbing because some medications given to cats such as doxycycline, tetracycline, propranolol, iron supplements, and bromide are known to cause esophageal lesions in experimental cats.[9,10]

Because many drugs are not in a form that is ideal for the species being treated (eg, cats, exotic animals, pet birds), the tablets have been crushed, capsules reformulated, and solutions altered to make a more convenient and palatable oral dosage form. However, when protective coatings are disrupted and vehicles are altered, the stability of the product may be compromised. In some instances, the only change is a slight alteration of pH. But, according to the *USP-National Formulary,* "improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug. A drug solution or suspension may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only 1 unit could decrease drug stability by a factor of 10 or greater."[11] Addition of a water-based solution to a product to create a liquid solution or a suspension results in the hydrolysis of certain compounds (eg, β-lactams, esters). Some drugs undergo epimerization (steric rearrangement) when exposed to a pH range higher than what is optimum for the drug; for example, this occurs to tetracycline when exposed to a pH higher than 3. Other drugs are oxidized, a reaction catalyzed by exposure to a high pH, rendering the drug inactive. Drugs most likely to be subject to oxidation are those with a hydroxyl group bonded to an aromatic ring structure. Oxidation may occur from exposure to light and oxygen during reformulation and mixing.

Veterinarians and pharmacists are obligated to be cognizant of the potential for interactions and interferences with stability. Oxidation is often visible through a color change (eg, color change to pink or amber). Loss of solubility may be observed through precipitation. Some drugs are prone to hydrolysis from moisture. A rule-of-thumb for veterinarians is that if a drug is packaged in blister packs or with a moisture-proof barrier, it is probably subject to loss of stability and potency if mixed with aqueous vehicles. If compounded formulations of solid dose forms show cracking, "caking," or swelling, the formulation has probably acquired moisture and may have lost potency. Another rule-of-thumb is that if the original packaging of a drug is in a light-protected or amber container, it is probably prone to inactivation by light. Vitamins, cardiovascular drugs, and phenothiazines are labile to oxidation from light during compounding. Also, as a general rule, if an antibiotic is available in a powder that must be reconstituted in a vial or in an oral dispensing bottle prior to administration, it should not be mixed with other drugs.

## Examples of Potential Problems

There are very few published studies in which drugs for veterinary patients have been tested for stability under the conditions used during compounding. Table 1 lists guidelines for potential problems. In a commercial formulation, the active ingredients and the excipients added to drug formulations are tested and must meet FDA-approved specifications to ensure the stability of the drug and uniformity in product in vivo performance. However, by adding other chemicals, flavorings, and vehicles, or by interfering with protective coatings of tablets, a compounder may interfere with the stability of the drug, thereby decreasing its potency, compromising its oral absorption, and consequently reducing its efficacy. There are published recipes in compounding journals, magazines, and handbooks, but few of these formulations have been tested for their stability and potency. Veterinarians have an obligation to question their compounding pharmacist about the stability and potency of formulations prepared for their patients and to insist on some valid documentation. When veterinarians compound formulations in their own practices, they should be cognizant of the potential interactions and alterations that may compromise product performance. Without proper equipment, it is difficult for most veterinary practices to perform reliable compounding.

There are a few published examples in which drug stability and efficacy have been compromised through compounding.

For example, when omeprazole was compounded for oral use in horses, it was not as effective for treating gastric ulcers as the commercial formulation registered for horses (Gastroguard).[12] Systemic absorption of the compounded formulation was lower than that of the proprietary product. Omeprazole is known for its instability, a problem minimized in the original formulation intended for use in horses or people.

Fluoroquinolone antibiotics are frequently modified for administration to exotic animals and horses. Our laboratory has evaluated the compatibility of enrofloxacin and orbifloxacin with flavorings, vehicles, and other ingredients. We found that, with few exceptions, this class of drugs is compatible with most mixtures, and remarkably stable. A notable exception is the chelation of enrofloxacin with aluminum-containing products (eg, antacids, sucralfate), resulting in a significant portion of the medication becoming unavailable for absorption. We also documented that certain mixtures and flavorings may be incompatible with fluoroquinolones if they contain metal ions that are known to cause chelation. For example, we found that if crushed orbifloxacin tablets are mixed with Lixotinic, a vitamin and mineral supplement that is sometimes used as a flavored vehicle for oral drug administration, orbifloxacin in vitro stability was reduced to half that seen with the original formulation. The decrease in drug stability was attributable to the high levels of iron contained within this flavorant (2.5 mg/mL). Other flavorings and vehicles (eg, corn syrup, molasses, fish sauce, and Syrpalta) had no affect on orbifloxacin absorption.

Antifungal drugs also are subject to instability. Itraconazole is frequently compounded from bulk drugs or the proprietary capsules. However, during compounding, inactivation may occur. Itraconazole is insoluble in water and cannot be formulated into aqueous vehicles. Itraconazole may also adsorb to plastic and glassware, decreasing product drug concentrations. Recently in our laboratory, a clinician requested an assay of a 100-mg capsule of itraconazole that was formulated by a compounding pharmacist. We found that the concentrations of itraconazole or the metabolite hydroxyitraconazole were undetectable from the compounded capsule.

Aminoglycoside antibiotics (gentamicin, tobramycin, and kanamycin) are inactivated when admixed with other antibiotics, particularly beta-lactams. This interaction is greatest with carbenicillin, followed by ticarcillin, penicillin G, and ampicillin. Loss of potency by as much as 50% can occur within 4 to 6 hours. This interaction is a potential problem when antibiotic mixtures are prepared and dispensed for use several hours later. This interaction does not occur at therapeutic concentrations within the patient because the drugs are diluted in plasma and body fluids.

Drugs formulated as acids—such as the hydrochloride form of basic drugs—are designed to maintain their solubility in aqueous solutions. However, when these formulations are mixed with drugs that are basic, or are added to basic vehicles, drug precipitation may occur.

Several drugs are not soluble in aqueous vehicles. Therefore, they are dissolved in organic solvents (propylene or polyethylene glycol, for example), or alcohols. These are notoriously unpalatable to some animals, particularly cats. However, if these formulations are diluted in aqueous fluids, precipitation may occur. When these are stored at home by the pet owner, precipitation of the drug to the bottom of the container results in the dosing of a dilute mixture when the container is sampled from the top and a highly concentrated mixture when the container is sampled from the bottom (assuming that the precipitate at the bottom can be resuspended). This also may be observed when mixing some drugs in aqueous fluids. For example, if diazepam solution (which contains propylene glycol and alcohols) is diluted in saline solution or Lactated Ringer's solution, precipitation may occur.

## The Interspecies Problem

### *Interspecies Differences in Oral Administration and Absorption*

Many drugs intended for one species (or humans) are frequently compounded for another veterinary species. In these instances, it is not only the compounding practice that may affect drug absorption, but also the species differences in drug pharmacokinetics. Although one assumes that absorption may be similar, differences can exist that may result in poor efficacy. Grass and Sinko[13] concluded that there is no apparent relationship when comparing bioavailability of orally administered drugs among humans, dogs, primates, and rodents. Therefore, for drugs administered orally, it is very difficult to broadly extrapolate the results from studies performed in people to predict product bioavailability in veterinary species. Specific studies are usually needed unless it is known that the drug is highly stable, has a high aqueous solubility, and is well absorbed under a variety of conditions. The influence of formulation on drug absorption and a review of the species differences in drug absorption were summarized in a 2-part review.[14,15] This review presents the basis for in vitro-in vivo correlations (IVIVC) for drugs administered to animals. It may be possible to predict drug absorption in animals based on the biopharmaceutics classification system (BCS), which categorizes drugs into 1 of 4 classes based on their aqueous solubility and membrane permeability.[16] In the future, guidelines may be developed to apply BCS principles to predict oral drug absorption in animals.

The differences in oral absorption can be partially explained by differences in anatomy and physiology.[17-19] Comparisons between oral absorption of drugs in humans vs dogs have been reviewed with the availability of rich data.[18,20,21] For

example, dogs have a shorter gastrointestinal transit time than people (2 hours vs 4 hours, respectively). However, dogs compensate with longer intestinal villi, which provide more surface area for absorption. Dogs have higher bile salt secretion, which increases the solubility of some poorly water-soluble drugs. A higher pH in the intestine of dogs results in better absorption of drugs that are weak bases. On the other hand, dogs (and probably cats) have lower basal acid secretion than people.[17,18] Many drugs are compounded for horses, but the glandular portion of the stomach (responsible for secreting acid) is proportionately smaller than that found in other animals, although the stomach and intestinal pH ranges are similar.[17] Horses use hindgut fermentation for digestion, and the ratio of intestine length to body length is intermediate between pigs and ruminants.[17]

## Transdermal Drugs

In some animals, transdermal delivery is ideal because it is convenient and bypasses the intestinal and hepatic first-pass effects. The medications most often formulated for transdermal delivery to animals are antiparasitic drugs for cattle, and antiflea drugs for dogs and cats. Transdermal applications of human drugs also have been used. One such delivery device consists of a patch containing a reservoir of fentanyl (Duragesic), which is absorbed through the skin. Studies from our laboratory showed that these patches can produce effective plasma fentanyl concentrations in dogs and cats.[22-24]

The administration of transdermal drugs to animals was reviewed recently.[25] Because of success with some transdermal drugs (antiparasitic agents and fentanyl), there is considerable interest in formulating a wide range of other drugs for this route. Compounding veterinary pharmacists advertise the ability to formulate transdermal medications from existing forms of antibiotics, cardiovascular drugs, antithyroid drugs, analgesics, corticosteroids, and antidepressants. Bulk drugs also have been used for transdermal compounding. Drugs have been combined with penetration enhancers to facilitate transdermal absorption. One popular example of a penetration enhancer is pleuronic lecithin organogel (PLO), which is lecithin (derived from eggs or soybeans) that is mixed with isopropyl palmitate and a poloxamer (Pluronic). The ingredients in PLO act as surfactants, emulsifiers, and solubilizing agents. Although the use of PLO is popular among the veterinary compounding pharmacies, there are no successful commercial formulations that have combined PLO with systemic drugs. Usually, animal owners are instructed to apply the drug to the inside of the animal's ear because this location cannot be licked with the tongue, and it is usually not covered with hair.

At the time of this writing, most published reports of transdermal application of drugs to cats showed that absorption was incomplete, nonexistent, or highly inconsistent among cats. Yet, via the Internet and promotion at national trade shows, some pharmacies widely advertise their willingness to provide these formulations to veterinarians. Drugs examined so far have included glipizide, dexamethasone, buspirone, amitriptyline, fentanyl, morphine, fluoxetine, and diltiazem.[26,27] Glipizide was absorbed poorly in cats, with bioavailability equaling only 4% to 30% of that observed from the oral formulation.[28] Fluoxetine transdermal bioavailability was only 10% of that compared with oral absorption of an approved human formulation. However, if a large dose was administered (10 times the oral dose), plasma concentrations equal to that achieved after oral administration were achieved,[29] although repeated topical application caused dermatitis. In a pharmacokinetic investigation, methimazole was shown to be poorly absorbed,[27,30] but a clinical investigation provided evidence of efficacy with repeated transdermal applications.[31,32] In the most recent study,[31] the authors showed that transdermal methimazole was not as effective as oral methimazole for treating hyperthyroid cats, but it may be an option for some cats that are difficult to medicate orally. Amitriptyline and buspirone administered transdermally to cats[33] showed negligible transdermal absorption. When dexamethasone was topically administered in PLO, there was negligible absorption in cats.[34] Other drugs that have been prepared in a PLO transdermal formulation are morphine, fentanyl, and enrofloxacin. Preliminary results indicate that transdermal absorption from these formulations was negligible. (References not yet available in a published article at the time of this article.)

The most common concern associated with these formulations is a lack of efficacy because of poor absorption or decreased drug stability. However, an increased risk of toxicity is also a potential problem. If the drug is ordinarily poorly bioavailable after oral administration because of a large first-pass effect, higher systemic levels after transdermal application may result. Obviously, there is also a risk to the animal owner applying the medication if the drug is toxic to humans.

## Current Guidelines for Veterinarians

Through the CPG, the FDA-CVM uses regulatory discretion to allow for veterinary drug compounding within the scope of veterinary clinical practice situations. However, some restrictions still apply, and individual states may impose requirements that are more restrictive than those found under federal law. Whenever possible, the source of the drug used for compounding should be an FDA-approved substance, and/or a *USP/NF* grade substance. Drugs must be compounded from the original formulation if an approved product exists. Compounding from bulk drugs is not allowed, especially if a proprietary registered formulation is available. Therefore, if a veterinary pharmacy compounds drugs from a bulk source, it may be engaging in an illegal practice. If bulk

drugs are used because no other forms are available, the pharmacist should use bulk substances registered with the FDA, and accompanied by a valid certificate of analysis.

It is the responsibility of the veterinarian and pharmacist to ensure that regulations and guidelines are being followed in order to have confidence in the compounded medication. The FDA Web site[4] lists the labeling requirements for compounded drugs. The *USP-NF* lists specific guidelines in the General Chapter on Pharmaceutical Compounding.[35] Often overlooked in compounding practices is the guideline to ensure that the compounded formulation is not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume. There are also guidelines for stability considerations in Table 1 and in the *USP-NF* chapter titled "Stability Considerations in Dispensing Practice."[11] Generally, the beyond-use dating for a compounded drug should not be later than 25% of the time remaining until the product's expiration date. For water-containing formulations, the beyond-use date is not later than 14 days at cold temperatures and, for all other formulations, not later than the intended duration of therapy or 30 days, whichever is earlier. These limits may be exceeded when there are supporting scientific data that apply to the specific compounded formulation.

## Future of Veterinary Drug Compounding

In recent months the FDA-CVM has more actively pursued veterinary compounding pharmacies that are clearly in violation of federal restrictions (www.avma.org/onlnews/javma/oct04/041001a.asp). Most of these investigations have involved pharmacies that either use bulk drugs to substitute for approved products, or engage in unacceptable compounding practices to produce medications for animals in mass quantity. Although the CVM-FDA's resources are limited, their enforcement of current guidelines may limit some current practices. Within a veterinary practice, veterinarians should consult available references whenever possible to ensure that compounded formulations are stable, potent, and safe. The *USP* guidelines, listed earlier, are helpful but do not absolve veterinarians from using common sense and their scientific backgrounds to recognize potential incompatible chemical mixtures. (All veterinarians in the United States are required to complete courses in chemistry prior to admission into veterinary school and are required to take pharmacology courses in the veterinary curriculum.)

It is anticipated that the USP will play a more active role in providing guidelines for veterinary compounding in the future. Information from USP can be found at www.usp.org. The USP has provided a new general chapter <1075> to the *United States Pharmacopeia 28* and the *National Formulary 23* pertaining to good compounding practices.[1] The new general chapter is intended to provide guidance on how to apply good compounding practices for the preparation of compounded formulations for humans and/or animals. Previous general chapters did not include information on drugs for animals, and this new general chapter is the first to indicate that compounded prescription drugs for animals shall be handled in a manner consistent with that associated with human drug prescriptions. There are additional plans to consider specific veterinary information in the *USP-NF* that may address information on specific formulations used in veterinary medicine. The new general chapter <1075>[1] is the result of the collaboration of USP's Expert Committees on Compounding Pharmacy, Parenteral Products, Compounding and Preparation, and the Compounding Pharmacy Project Team. This general chapter includes detailed information on compounding, responsibilities of the compounder, training required, compounding procedures and documentation, drug compounding facilities and equipment needed, component selection requirements, packaging and drug product containers, and compounding controls for labeling.

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